Current Issues Regarding Sterility Assurance Submissions for Sterile Generic Drug Products

Dr. Lynne A. Ensor

U.S. Food & Drug Administration
Center for Drug Evaluation & Research
Office of Pharmaceutical Science/Office of Generic Drugs
Microbiology Team Leader

2011 GPhA/FDA Fall Technical Conference
October 5, 2011

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

OGD Division of Microbiology

- Division Created
- Division structure still pending

Agenda

- Justification of Terminal Sterilization vs. Aseptic Fill
- Validation of Sterilizing Filter
- In-process Testing
- Microbiological Quality following Product Penetration
- Antimicrobial Effectiveness Test
- Update on Finished Product Specifications & Tests
  - Sterility Test
  - Endotoxins Test
- Stability Protocol Clarification
  - Sterility vs. Container Container Closure Integrity
- Positron Emission Tomography Drugs

Justification for Terminal Sterilization vs. Aseptic Fill

- Historically:
  - Proposed rule: 1991
    - 21 CFR Parts 211, 313 and 514: Use of Aseptic Processing and Terminal Sterilization in the Preparation of Sterile Pharmaceuticals for Human and Veterinary Use
  - Withdrawal of Proposed Rule: 2004
    - FR Doc 04-26234 (11/26/04, vol. 69, no. 227)

Justification for Terminal Sterilization vs. Aseptic Fill (2)

- Withdrawal of the proposed rule doesn't change current thinking, although it reduces it to a policy rather than regulation

- GFI: Sterile Drug Products Produced by Aseptic Processing – CGMP
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

  It is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible. However, some final packaging may afford some unique and substantial advantage (e.g., some dual-chamber syringes) that would not be possible if terminal sterilization were employed. In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility assurance.

Justification for Terminal Sterilization vs. Aseptic Fill (3)

- ICH Q8
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

  For those products intended to be sterile an appropriate method of sterilization for the drug product and primary packaging material should be chosen and the choice justified.

- The suitability of the justification for the sterilization method is a review decision

Validation of the Sterilizing Filter

- For Production
  - Fully describe production process
    - Redundant filters or pre-filters
    - Filter porosity
    - Integrity test and acceptance criteria
    - Volume, flow rate, pressure, max. duration of filtration
- For Bacterial Retention Study
  - Summary of Test method and Data
    - Should simulate production condition (scaled-down)
  - Filter Integrity Specifications
    - Minimum Bubble Point Consideration

In-process Testing

- Bulk Drug Solution Bioburden
  - Pre-sterilization
  - Describe any holding parameters
  - Test method
  - Action level
    - Based on historical data, if available
    - Typically NMT 10 cfu/mL or lower

In-process Testing

- Environmental Monitoring
  - Sampling
    - Air, Surfaces, Personnel, WFI, Yeast/molds/anaerobes
  - Alert/Action levels
  - Actions taken in response to exceeded levels investigation description
    - Organism ID
    - Notification of appropriate management
    - Corrective/preventative actions
    - Trend analysis

Microbiological Quality following Product Penetration

- Post-reconstitution or dilution

- Risk assessment data to support the proposed post-penetration holding parameters per product labeling

Microbiological Quality following Product Penetration – References

- **Guidance for Industry: ICH Q8 Pharmaceutical Development**
  - Section 2.5 - Microbial Attributes:

    "Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented in this section."

- **Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products**
  - "Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points, and ...."

- **Guidance for Industry: ICH Q9 Quality Risk Management**
  - It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies.

Microbiological Quality following Product Penetration – References (2)

- ***Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration***
  - Metcalfe, J. Am. Pharm. Review, Jan./Feb. 2009, p. 84- 89.
- ***Evaluation of the Microbial Growth Potential of Pharmaceutical Drug Products and Quality by Design***
  - Lolas, A. G. & J. W. Metcalfe. PDA J Pharm Sci and Tech. 2011. 65: 63-70.

Microbiological Quality following Product Penetration

- May base study on USP <51>
  - Compendial organisms
  - Typical skin microflora
  - Noscomial infections
- May require various storage conditions and/or reconstitution solutions
  - May bracket based on likelihood to promote microbial growth

Antimicrobial Effectiveness Test

- Typically USP <51>
- For multi-dose products, regardless of whether or not preservative is in drug
  - If not labeled single or multi- dose, does product volume allow for multiple doses?
- If no preservative in product, use minimal API concentration from release/stability specification

Sterility Testing

- Per USP <71> or equivalent method
- Stability Test Alternative - Container/Closure Integrity Testing
  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM146076.pdf
- At release and annually on stability until product expiry
- USP Microbiology Committee of Experts
  - Study alternatives to the growth/turbidity-based sterility test in current chapter <71>

Bacterial Endotoxins Test

- Method
  - USP <85> or equivalent
- Specification
  - NMT 5.0 EU/kg/hr for parenterals (except those administered intrathecally and on a body surface area basis)
  - NMT 0.2 EU/kg/hr for intrathecally administered products
  - NMT 2.5 EU/kg/hr for drugs administered on a body surface area basis (typically anticancer products)
  - Maximum labeled dose & duration of dosing
    - Maximum dose may be pediatric
  - USP specification may not meet specification requirements since endotoxin exposure/dose is based on current product labeling

Bacterial Endotoxins Test

- **RETIRED**
  - *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices* – 1987
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124785.htm
    - See Questions #8 & #9
- Guidance for Industry: Pyrogen and Endotoxins Testing Questions and Answers
  - TBA

Container Closure Integrity Testing

- Frequency – depends upon intention of test
  - 1 x validation test
  - Annually for stability samples, if being used in lieu of sterility testing
    - Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products

    http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM146076.pdf

- Methods
  - Dependent upon product & C/C system
    - Liquid, lyophilized, etc.

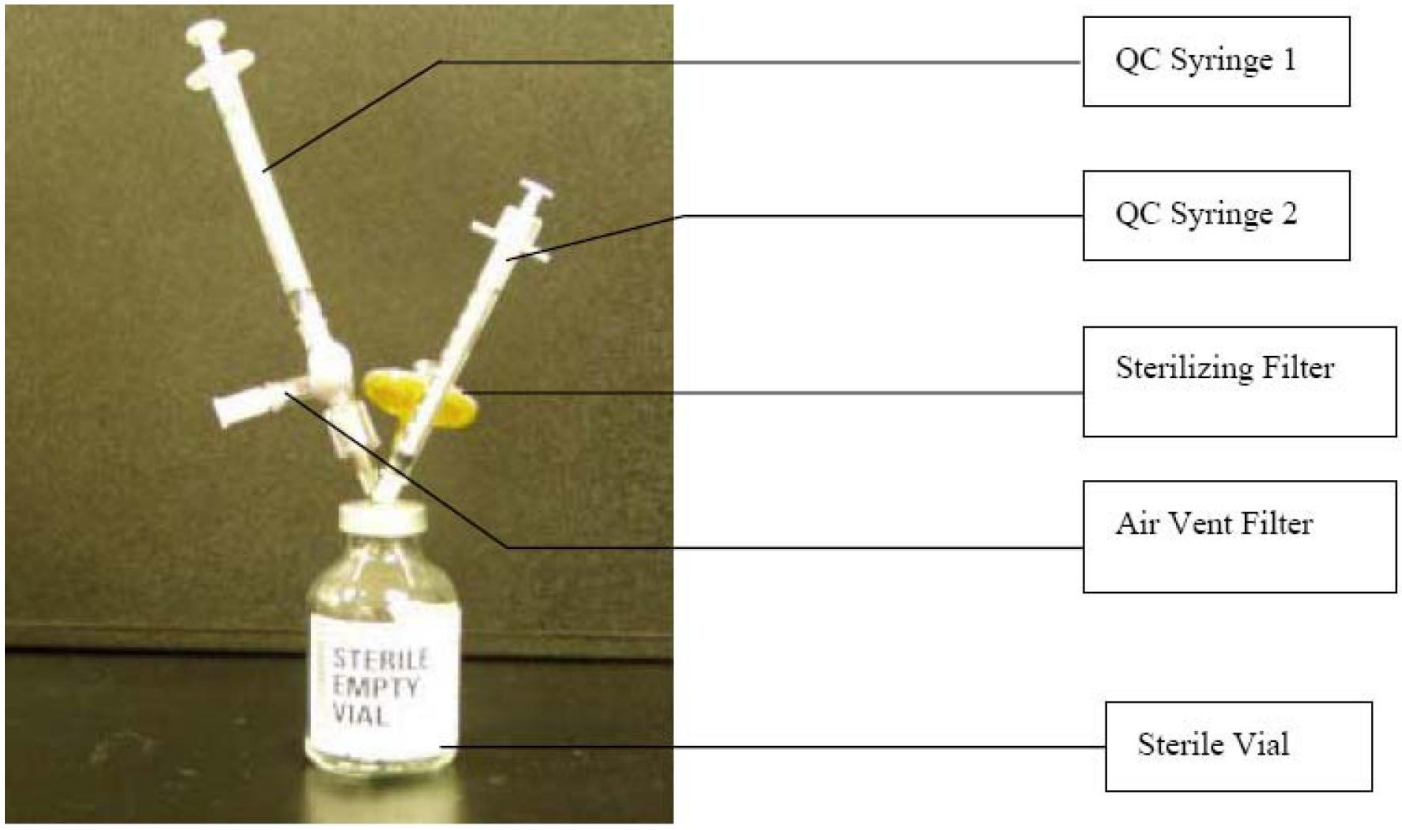
Positron Emission Tomography (PET)

- Group of radioactive drug product clinically used for imaging
- Very Short Half life
- Manufactured using cyclotron, typically in hospital pharmacy
- Drugs
  - Fludeoxyglucose F 18 Injection
  - Ammonia N 13 Injection
  - Sodium Fluoride F 18 Injection
  - Rubidium Rb 82 Injection

PET – Manufacture

PET – Manufacture

Figure 1: Completed vial assembly (30ml vial)



PET – Regulatory History

- 11/21/97 – Clinton signs Food & Drug Administration Modernization Act of 1997
  - Section 121(c) of the Act directs FDA to regulate PET drugs
    - Develop cGMPs
    - Consult with patient advocacy groups, professional associations, manufacturers, and persons licensed to make or use PET drugs during establishing procedures and requirements
    - Cannot require submission of NDAs or ANDAs for PET drugs that are not adulterated for 4 years after enactment or 2 years after FDA approved procedures and CGMP requirements for PET drugs (whichever is longer)

PET – Regulatory History (2)

- Dec. 9, 2009: FDA issued final CGMP regulations for PET products
- PET NDAs or ANDAs should be submitted to the Agency before 12/12/2011 – CFR Part 212s effective
- Potential for large influx of generic applications (ANDAs)

PET – Sterility Assurance Review of Applications

- Part of CMC
- Microbiology is separate discipline from Chemistry
- Focus on sterility assurance and endotoxins
- NDAs reviewed by OPS Microbiology Group
- ANDAs reviewed by OGD Division of Microbiology

PET – Microbiology Release Tests

- **Sterility Test –**
  - Product may be released/administered before the test is finished: 21CFR 211.165(a) and 21 CFR 212.70
  - Initiate test within 30 hours after completion of production*
  - Individually tested product samples, not pooled
  - After successful sterility test record is established for a particular PET drug, it is only necessary to test the first batch prepared each day

*30-hour requirement may be exceeded due to a weekend or holiday, if demonstrated that longer period does not adversely affect the sample or test results and sample is stored appropriately (e.g., under refrigeration).

PET – Microbiology Release Tests

- **Bacterial Endotoxins Test –**
  - Product Specification – NMT 175 EU/V, where V is the maximum volume of injection in mL
  - Testing performed and completed prior to release for human use

PET – Guidances & References

- USP <823> - Radiopharmaceuticals for Positron Emission Tomography – Compounding
- 21 CFR 212 – effective 12/12/11
- Guidance: PET Drug Applications – Content and format for NDAs and ANDAs (8/11)
  - Fludeoxyglucose F 18 Injection
  - Ammonia N 13 Injection
  - Sodium Fluoride F 18 Injection

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078738.pdf

PET – Guidances & References (2)

- Guidance: PET Drugs – Current Good Manufacturing Practice (CGMP) – 12/09

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070306.pdf

- Guidance: Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET Drugs) – Draft routed for clearance

- Guidance: PET Frequently Asked Questions - Draft

References

- *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf

- *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

References (2)

- *Guidance for Industry: Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Process*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072180.pdf

- *Guidance for Industry: Changes to an Approved NDA/ANDA*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf

Contact Information

Lynne A. Ensor, Ph. D

240-276-8827

lynne.ensor@fda.hhs.gov